

Clinical Effectiveness of Idarucizumab in Dabigatran Reversal

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ABSTRACT

AIM: Idarucizumab is a specific reversal agent for dabigatran. This study aims to evaluate the effectiveness and safety of idarucizumab in the reversal of dabigatran's anticoagulant effects in clinical practice.
METHODS: This was a multi-centered, retrospective cohort study of patients hospitalized with a major bleed and taking dabigatran

prior to admission. The intervention group of this cohort included patients who received idarucizumab. The control group included patients who did not receive idarucizumab and had an ICD-10 code for hospital admission involving a bleeding event and preadmission diagnosis of atrial fibrillation.

RESULTS: A total of 20 cases were included in the idarucizumab group and 18 cases in the control group. A greater proportion of patients receiving idarucizumab had achieved normalized activated partial thromboplastin time within 24 hours (100% vs. 0%; $p = 0.005$) and there was a trend towards fewer patients having received a transfusion of blood products compared to control (45.0% vs. 72.2%; $p = 0.171$). Length of hospital stay, in-hospital mortality and the proportion of patients that experienced a stroke, venous thromboembolism, hypersensitivity reaction, or ICU admission occurring in-hospital within 30 days were non-statistically different between the 2 groups.

CONCLUSION: The use of idarucizumab for the reversal of dabigatran for the management of major bleeding was effective in normalizing activated partial thromboplastin time. The trend towards lower rates of transfusion and higher rates of stroke or venous thromboembolism events with idarucizumab requires ongoing assessment. Future studies should continue to include transfusion rates and thrombotic events as outcome when assessing idarucizumab.

Key words: Hemorrhage; Dabigatran; Idarucizumab

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INTRODUCTION

Dabigatran is a competitive, reversible, direct thrombin inhibitor indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and for the prevention and treatment of venous thromboembolism (VTE)^[1]. Patients

anticoagulated with dabigatran may need emergent or urgent surgery; or suffer from trauma or acute conditions that cause life-threatening bleeding^[1]. Rapid reversal of anticoagulation may be required for these patients.

Prior to idarucizumab, there was no approved drug for dabigatran reversal^[2]. Various blood products have been studied for their role as anticoagulation reversal strategies for patients on dabigatran. Early studies were mostly limited to laboratory studies with a small sample of healthy volunteers, making it difficult to conclude the impact and role with blood product use in setting of dabigatran reversal^[3,4]. Moreover, the potential risk of thromboembolic events in patients treated with clotting factors for direct oral anticoagulant (DOAC) reversal is inconclusive, leading to interest in the use of specific reversal agents^[5].

Idarucizumab is a monoclonal antibody that binds to dabigatran with 300 times higher affinity compared to thrombin, but without intrinsic thrombin activity^[6]. It was approved by Health Canada in May 2016 and approved in the United States in 2015 as a reversal agent specific to dabigatran; and has been available for use across Vancouver, British Columbia area hospitals since November 2016. Idarucizumab has also been given a class IB recommendation for the reversal of dabigatran in the context of life-threatening bleeding or urgent surgery in the recent 2019 American Heart Association (AHA) atrial fibrillation guidelines update^[7]. This recommendation is based on the REVERSE-AD trial, a single-armed prospective study evaluating the use of idarucizumab in the urgent reversal of dabigatran and demonstrated rapid reversal of laboratory parameters^[2,7].

To date, there is limited comparative data to evaluate the effectiveness of this novel drug in the clinical setting. This study aims to evaluate the clinical effectiveness and safety of idarucizumab in the reversal of dabigatran's anticoagulant effects in major bleeding.

METHODS

This was a multi-centered, retrospective cohort study of patients that were admitted to an acute care hospital in Vancouver, BC, Canada and were anticoagulated with dabigatran prior to hospital admission. Inclusion criteria for the idarucizumab group (intervention group) were patients who were taking dabigatran prior to admission and received idarucizumab at an acute care hospital site between January 1st, 2016 and March 31st, 2018. The list of patients that received idarucizumab was compiled through the electronic hospital pharmacy record systems used at the respective health authorities.

The historical control group included patients that were admitted to an acute care hospital in Vancouver between October 1st 2014 to March 31st 2018 with an ICD-10 code for bleed (Appendix 1) and preadmission diagnosis of atrial fibrillation (ICD-10 code I48). These patients were taking dabigatran prior to admission and did not receive idarucizumab during their hospitalization.

Patients in both cohorts were excluded if they were not experiencing a major bleed at the time of required urgent anticoagulation reversal. Major bleeding was classified as per the International Society of Thrombosis and Haemostasis (ISTH) definition, which includes fatal bleeding, symptomatic bleeding in a critical area or organ, bleeding causing a fall in hemoglobin levels of 20g/L or more, or bleeding leading to transfusion of 2 or more units of whole blood or red cells.

Outcomes

The primary outcomes in this cohort study include: (1) Proportion

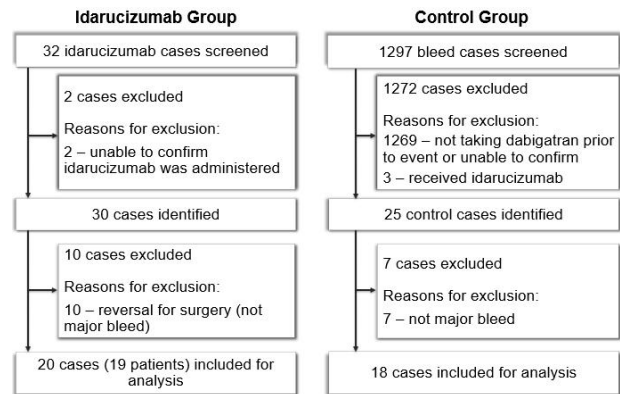


Figure 1 Selection of Study Participants.

Table 1 Baseline Characteristics.

	Idarucizumab (N=20)	Control (N=18)
Age - mean (SD) - years	77.6 (±10.5)	81.7 (± 6.2)
Male- no. (%)	14 (70.0)	11 (61.1)
Indication for Dabigatran		
Atrial Fibrillation - no. (%)	19 (95.0)	18 (100.0)
Treatment of VTE - no. (%)	1 (5.0)	0 (0)
Comorbidities		
Atrial Fibrillation	19 (95.0)	18 (100.0)
Hypertension	14 (70.0)	13 (72.2)
Diabetes	7 (35.0)	7 (38.9)
Dyslipidemia	6 (30.0)	7 (38.9)
CHF	5 (25.0)	4 (22.2)
COPD	4 (20.0)	5 (27.8)
History of Stroke	4 (20.0)	3 (16.7)
Dementia	4 (20.0)	0 (0)
History of MI	3 (15.0)	5 (27.8)
CKD	2 (10.0)	2 (11.1)
Dabigatran Dose		
110mg twice daily - no. (%)	12 (60.0)	11 (61.1)
150mg twice daily - no. (%)	7 (35.0)	5 (27.8)
Others or unknown - no. (%)	1 (5.0)	2 (11.1)
Time of last dose prior to admission		
< 12 hrs - no. (%)	3 (15.0)	0 (0)
> 12 hrs - no. (%)	4 (20.0)	7 (38.9)
Unknown - no. (%)	13 (65.0)	11 (61.1)
Baseline Laboratory Studies		
SrCr - mean (SD) - µmol/L	126 (±94)	101 (±48)
eGFR - mean (SD) - mL/min	57 (±23)	63 (±24)
aPTT - mean (SD) - sec	49 (± 18) [n=18]	55 (±19) [n=8]

Table 2 Location of Bleed.

	Idarucizumab (N=20)	Control (N=18)
Cerebrovascular - no. (%)	9 (45.0)	1 (5.6)
SAH - no.	2	0
ICH - no.	7	1
Respiratory - no. (%)	0 (0)	1 (5.6)
Abdominal - no. (%)	2 (10.0)	0 (0)
Gastrointestinal - no. (%)	7 (35.0)	16 (88.9)
Trauma - no. (%)	1 (5.0)	0 (0)
Source NYD - no. (%)	1 (5.0)	0 (0)

Table 3 Outcomes.

	Idarucizumab (N=20)	Control (N=18)	P-value
aPTT normalization within 24 hours - no. (%)	[n=8] 8 (100.0)	[n=4] 0 (0)	0.005
Received Blood Product - no. (%)	9 (45.0)	13 (72.2)	0.171
PRBC - median (IQR) - units	0 (0 - 3)	2 (0 - 3)	
Plasma - median (IQR) - units	0 (0)	0 (0)	
Platelet - median (IQR) - units	0 (0)	0 (0)	
Decrease in Hgb - no. (%)	[n=15] 9 (60.0)	[n=9] 4 (44.4)	0.751
Length of stay - median (IQR) - days	10 (4 - 20)	8 (6 - 18)	0.476
Stroke, venous thromboembolism, hypersensitivity reaction to intervention, or ICU admission within 30 days† - no. (%)	6 (30.0)	3 (16.7)	0.56
Stroke - no. (%)	2 (10.0)	1 (5.6)	
Venous thromboembolism - no. (%)	2 (10.0)	0 (0)	
Hypersensitivity reaction - no. (%)	1 (5.0)	0 (0)	
ICU admission - no. (%)	1 (5.0)	3 (16.7)	
In-hospital mortality - no. (%)	7 (35.0)	5 (27.8)	0.898

† Proportion of patients experiencing a stroke, venous thromboembolism, hypersensitivity reaction to intervention, or ICU admission in hospital within 30 days.

of patients with elevated activated partial thromboplastin time (aPTT) at baseline achieving normalized aPTT within 24 hours of receiving either idarucizumab (intervention group) or supportive therapy (control group); (2) Proportion of patients requiring the use of any blood product during admission within 30 days; (3) Proportion of patients with decrease in hemoglobin (Hgb) between baseline and 12 hours after receiving either idarucizumab (intervention group) or supportive therapy (control group).

Baseline laboratory values were taken as the most recent value available prior to receiving either idarucizumab (intervention group) or supportive therapy (control group).

The secondary outcomes include: (1) Proportion of patients experiencing either a stroke, venous thromboembolism, hypersensitivity reaction to intervention, or ICU admission in hospital within 30 days; (2) Duration of hospital stay. (3) All cause in-hospital mortality rate.

This research protocol was approved by the University of British Columbia, Vancouver Coastal, Providence Health Care and Fraser Health Care Research Ethics Boards. No funding was obtained for this research study.

Statistical Analysis

Descriptive statistics were used for the analysis of patient demographic data, including the mean or median, along with the standard deviation (SD) and interquartile range (IQR) respectively. Unpaired t-test was used in the analysis of continuous data outcomes and chi-square was used for the analysis of categorical data. Statistical analysis was completed using Microsoft Excel and GraphPad, and a p-value of <0.05 was considered to be statistically significant.

RESULTS

Demographics

A total of 1,329 patients were screened. There were 30 cases of idarucizumab use during hospitalization (idarucizumab group) and 25 cases of a bleeding event in patients taking dabigatran prior to admission for atrial fibrillation but did not receive idarucizumab (historical control group) identified. The primary reason for exclusion during screening was due to either patients not taking dabigatran prior to admission or lack of documentation to confirm dabigatran

use prior to hospitalization (Figure 1). Ten cases in the idarucizumab group were excluded as the patients received idarucizumab for the indication of reversal prior to surgery rather than for major bleed, and 7 cases in the control group were excluded as the patients did not meet our definition for major bleed. The final analysis included 20 cases in the idarucizumab group and 18 cases in the control group.

Baseline patient characteristics are outlined in Table 1. The mean age, proportion of male patients, dabigatran dose and baseline comorbidities were similar between groups. The time of the last dabigatran dose prior to hospitalization is known only in approximately 35% of cases in both groups, with the majority having taken dabigatran greater than 12 hours prior to receiving an intervention. A greater proportion of patients experienced a cerebrovascular bleed in the idarucizumab group (45.0% vs. 5.6%) and fewer experienced a gastrointestinal bleed (35.0% vs. 88.9%) compared to the control group (Table 2).

Outcomes

Given the retrospective nature of our study, only 8 patients out of 20 in the intervention group and 4 patients out of 18 in control group with an elevated baseline aPTT had a repeat aPTT drawn within 24 hours. Of these available patients, the proportion of patients who achieved normalization of aPTT within 24 hours was significantly greater in the idarucizumab group as compared to the control group (Table 3). Although not statistically significant, there was a trend towards fewer patients in the idarucizumab group that received a transfusion of blood products compared to control (45.0% vs. 72.2%; $p=0.171$), driven by the use of packed red blood cells (PRBC) transfusion. Two patients received plasma and platelet transfusions in addition to PRBC in the idarucizumab group, and one patient received plasma transfusion in the control group. Fifteen out of the 20 patients in the intervention group and 9 out of the 18 patients in the control group had a repeat Hgb drawn within 12 hrs from receiving either idarucizumab (intervention group) or supportive intervention (control group). A decrease in Hgb was observed in 60% of patients in the idarucizumab group as compared to 44.4% of patients in the control group.

For the secondary outcome of stroke, venous thromboembolism, hypersensitivity reaction to intervention or ICU admission, there was no statistical difference between the idarucizumab and control group. Similarly, there was no difference between the idarucizumab

and control group in respect to length of hospital stay and in hospital mortality. One patient in the idarucizumab group did not receive the complete 5g dose of idarucizumab due to suspected hypersensitivity reaction and ultimately expired due to major bleeding.

DISCUSSION

Our results confirm previously published literature establishing that the use of idarucizumab rapidly reverses the anticoagulant effects of dabigatran based on hematological measures, with 100% of the patients who received idarucizumab in our study having achieved normalized aPTT within 24 hours. This is comparable to the REVERSE-AD trial which demonstrated normalization of blood diluted thrombin time (dTT) in 98% of the patients, as well as reversal of elevated ecarin clotting time (ECT) and aPTT^[2]. While it was not found to be statistically significant, the trend towards lower transfusion rates in the idarucizumab group noted our study adds a finding that the use of idarucizumab could potentially be associated with a reduced need for administration of blood products, mainly PRBC, as compared to supportive management alone. This outcome was also noted in a recently published retrospective comparative study of idarucizumab by Singh *et al* which found reduced use for transfusions associated with the use of idarucizumab in patients experiencing a gastrointestinal bleed^[8]. This could be clinically important, as blood transfusions can also be associated with the risks such as transfusion reactions, infection, and acute lung injury^[9].

Thrombotic events have been reported in the REVERSE-AD trial and other case series involving idarucizumab use with event rates ranging from 0% to 36%^[10-14]. There appears to be a trend towards higher rates of stroke or venous thromboembolism (VTE) in the idarucizumab group compared to control (20% vs. 5.6%) in our cohort of patients, although this was not statistically significant and could be variation due to chance from the small sample of cases available. On the contrary, Singh *et al* had observed lower VTE rate along with higher in-hospital mortality rate in patients receiving idarucizumab for intracranial bleeds, but possible trend towards higher VTE rate with idarucizumab use for gastrointestinal bleeds^[8]. Thus, the effect of idarucizumab on this safety outcome remains inconclusive and should continue to be monitored with future research.

While the length of hospital stay was longer in the idarucizumab group, this was not statistically different from the control group. Similarly, there was no difference between both groups in respect to hospital mortality. It is noteworthy, that the rates of in hospital mortality in both groups were quite high in our study, ranging 28-35%. The 30-day mortality rate in the REVERSE-AD trial was 13.5% in those with major bleeding and 12.6% in those requiring urgent surgery^[2]. In hospital mortality rate in other case series have ranged from 0% to 36%, but several of the case series had included patients receiving idarucizumab prior to thrombolysis, an indication that has not yet been approved for the drug and with limited available literature to describe its use^[11-14].

Our study does have several limitations. First, being a retrospective cohort study, there are confounding factors that could influence the results. The idarucizumab group predominantly consisted of patients experiencing a cerebrovascular bleed while the control group mostly consisted of gastrointestinal bleeds. This suggests that the idarucizumab group may have included patients with a higher risk of adverse outcomes based on the location of their bleed. This difference is potentially contributed by selection bias, whereby patients who experienced a more severe bleed or demonstrated hemodynamic instability may bias clinicians towards administering idarucizumab.

As well, while there are defined criteria for major bleeding, patients can be very heterogenous in their presentation and commonly, multiple interventions are used concurrently to manage a major bleed. This would make identification of a single intervention, such as administration of idarucizumab, difficult to delineate. Furthermore, the number of patients in both the intervention group and control group that had a repeat aPTT and Hgb available after admission was less than the total number of patients in their respective groups. This lack of complete data on all patients reflects the retrospective design of the study.

Secondly, our study had a small sample size, thus it may not have sufficient power to detect any statistically significant differences in clinical outcomes, such as length of hospital stay and mortality. Over the 2 years course of our study across multiple hospitals, we identified only 20 patients who were hospitalized and received idarucizumab for the management of major bleeding while taking dabigatran. The control group had only 18 patients that were hospitalized for a bleeding event and were taking dabigatran prior to admission but did not receive idarucizumab.

Finally, one of our main outcomes was normalization of aPTT. Studies assessing the effect of dabigatran on various coagulation assays have shown that aPTT does not correlate to dabigatran's anticoagulant activity as strongly as other measures such as ECT or dTT^[15]. However, the efficacy of idarucizumab in the reversal of aPTT have also been well reported in laboratory studies and numerous case reports^[2,5,10-14]. The choice of aPTT as an outcome for our study was due to the limited availability of routine dTT and ECT laboratory assays at our included acute care hospitals, thus a limitation of our retrospective design. INR and aPTT are the coagulation parameters most commonly available at most hospital sites and aPTT remains a practical tool for the rapid qualitative assessment of dabigatran's anticoagulant effect^[15,16].

CONCLUSION

In our retrospective study, the use of idarucizumab for the reversal of dabigatran in the management of major bleeding was effective in normalizing laboratory coagulation markers (aPTT). The trend towards potentially reduced need for blood transfusions and higher stroke or venous thromboembolism events requires ongoing assessment. Future studies should continue to include transfusion rates and thrombotic events as clinical outcome in the assessment of idarucizumab.

CONFLICTS OF INTEREST

Katherin Badke reports grants from Vancouver Coastal Health Research Challenge outside the submitted work; the remaining authors declare no potential conflicts of interest.

REFERENCES

1. Pradaxa (dabigatran etexilate): Capsules 75mg, 110mg and 150mg [product monograph]. Boehringer Ingelheim Pharmaceuticals, Inc. 2016 Aug 11.
2. Pollack CV Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, *et al.* Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. *N Engl J Med.* 2017;377(5):431-441. [DOI: 10.1056/NEJMoa1707278]; [PMID: 28693366]
3. Hayes BD, Winters ME, Rosenbaum SB, Allehyani MF, Vilke GM. What is the Role of Reversal Agents in the Management of Emergency Department Patients with Dabigatran-Associated Hemorrhage? *J Emerg Med.* 2018;54(4):571-575. [DOI:

- 10.1016/j.jemermed.2017.12.061]; [PMID: 29456085]
4. Tornkvist M, Smith JG, Labaf A. Current evidence of oral anticoagulant reversal: A systematic review. *Thromb Res.* 2018;162:22-31. [DOI: 10.1016/j.thromres.2017.12.003]; [PMID: 29258056]
 5. Andresen K, Atar D, Gjertsen E, Ghanima W, Roseth S, Johansen OE. Mechanisms of action and clinical use of specific reversal agents for non-vitamin K antagonist oral anticoagulants. *Scand Cardiovasc J.* 2018;52(3):156-162. [DOI: 10.1080/14017431.2018.1453613]; [PMID: 29569500]
 6. Praxbind® (idarucizumab): 5g IV injection [product monograph]. Boehringer Ingelheim Pharmaceuticals, Inc.;2015.
 7. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2019;74(1):104-132. [DOI: 10.1016/j.jacc.2019.01.011]; [PMID: 30703431]
 8. Singh S, Nautiyal A, Belk KW. Real World Outcomes Associated with Idarucizumab: Population-Based Retrospective Cohort Study. *Am J Cardiovasc Drugs.* 2020;20(2):161-168. [DOI: 10.1007/s40256-019-00360-6]; [PMID: 31332727]
 9. Goodnough LT. Risks of blood transfusion. *Crit Care Med.* 2003;31(12 Suppl): S678-86. [DOI: 10.1097/01.CCM.0000100124.50579.D9]; [PMID: 14724466]
 10. Lu VM, Phan K, Rao PJ, Sharma SV, Kasper EM. Dabigatran reversal by idarucizumab in the setting of intracranial hemorrhage: A systematic review of the literature. *Clin Neurol Neurosurg.* 2019;181:76-81. [DOI: 10.1016/j.clineuro.2019.04.013]; [PMID: 31015061]
 11. Tsai LK, Lin HJ, Chua SK, Liao PC, Yang YP, Chou PC, et al. Real-World Experience with Idarucizumab to Reverse Anticoagulant Effect in Dabigatran-Treated Patients: Report of 11 Cases from Taiwan. *J Stroke Cerebrovasc Dis.* 2018;27(2):e27-e33. [DOI: 10.1016/j.jstrokecerebrovasdis.2017.09.044]; [PMID: 29122465]
 12. Vosko MR, Bocksrucker C, Drwiła R, Dulicek P, Hauer T, Mutzenbach J, et al. Real-life experience with the specific reversal agent idarucizumab for the management of emergency situations in dabigatran-treated patients: a series of 11 cases. *J Thromb Thrombolysis.* 2017;43(3):306-317. [DOI: 10.1007/s11239-017-1476-2]; [PMID: 28210988]
 13. Kermer P, Eschenfelder CC, Diener HC, Grond M, Abdalla Y, Althaus K, et al. Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany - A national case collection. *Int J Stroke.* 2017;12(4):383-391. [DOI: 10.1177/1747493017701944]; [PMID: 28494694]
 14. Raco V, Ahuja T, Green D. Assessment of patients post reversal with idarucizumab. *J Thromb Thrombolysis.* 2018;46(4):466-472. [DOI: 10.1007/s11239-018-1723-1]; [PMID: 30120649]
 15. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, et al. Dabigatran etexilate--a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost.* 2010;103(6):1116-27. [DOI: 10.1160/TH09-11-0758]; [PMID: 20352166]
 16. Hapgood G, Butler J, Malan E, Chunilal S, Tran H. The effect of dabigatran on the activated partial thromboplastin time and thrombin time as determined by the Hemoclot thrombin inhibitor assay in patient plasma samples. *Thromb Haemost.* 2013;110(2):308-15. [DOI: 10.1160/TH13-04-0301]; [PMID: 23783268]